REMARKS

In view of the above amendment and the following remarks, reconsideration of the outstanding office action is respectfully traversed. Pursuant to 37 CFR § 1.21, attached as an appendix is a version with markings to show changes made to the specification and the claims.

Neural progenitor cells persist throughout the adult forebrain ventricular zone, and have been found in species ranging from canaries to humans. To the extent that neurogenesis and oligoneogenesis by these endogenous progenitors may be induced or supported exogenously, these cells may provide a cellular substrate for repair in the adult central nervous system (CNS). In culture, adult-derived progenitors have been found to respond to mitogens, in particular epidermal growth factor (EGF) and fibroblast growth factor 2 (FGF2), with increased division and neuronal mitogenesis. Furthermore, neurons generated from them respond to brain-derived neurotrophic factor (BDNF) with enhanced migration, maturation, and survival *in vitro*. Similarly, infusions of EGF and FGF2 into the adult ventricular system stimulate mitotic gliogenesis and neurogenesis, respectively, while intraventricular infusions of BDNF can enhance neuronal migration to the olfactory bulb, rostral migratory stream and adjacent forebrain. Although intriguing, these studies have been limited by the need for chronic intraventricular catheterization, with its dependence upon protein availability and stability, the uncertain tissue bioavailability of intraventricularly administered proteins, and the risks of infection and catheter loss inherent in chronic ventriculostomy.

The striatum is the major target of the progressive neurodegeneration that occurs in Huntington's Disease, in which the major neuron loss is that of the striatal GABA-producing neurons. Other degenerative diseases, such as amyotrophic lateral sclerosis (ALS; also known as Lou Gehrig's Disease), and progressive muscular atrophy, result at least in part from a decay of motor neurons which are located in the ventral horn of the spinal cord.

While there are some therapies available to treat the symptoms and decrease the severity of such diseases (e.g., L-dopa to treat Parkinson's Disease), there currently exists no effective treatment to prevent or reduce the degeneration of most of the above-mentioned classes of affected neurons, or to promote their repair. Several naturally-occurring proteins have been identified based on their trophic

activity on various neurons. These molecules are termed "neurotrophic factors". Neurotrophic factors are endogenous, soluble proteins that can stimulate or regulate the production, survival, growth, and/or morphological plasticity of neurons.

The known neurotrophic factors belong to several different protein superfamilies of polypeptide growth factors based on their amino acid sequence homology and/or their three-dimensional structure. One family of neurotrophic factors is the neurotrophin family. This family currently consists of nerve growth factor (NGF), BDNF, neurotrophin-3 (NT-3), neurotrophin-4 (NT-4), and neurotrophin-6 (NT-6).

On the basis of current studies, and of their limitations in practice, it will be appreciated that a need exists for an efficient means of delivering neurotrophic differentiation agents to the adult ventricular zone, the site of residual progenitor cells in the adult brain. Furthermore, in view of the fact that many nervous system disorders and diseases have no known cure, there is a need in the art for new methods of inducing neuronal production in the adult brain, especially for treating Huntington's Disease and other degenerative neurological conditions, as well as stroke and traumatic brain injury.

The present invention is directed to overcoming these and other deficiencies in the art.

The objection to claims 6 and 18 are respectfully traversed in view of the above amendments.

The rejection of claims 28-30, 33-40, and 44-47 under 35 U.S.C. § 112 (1st para.) for lack of enablement is respectfully traversed.

To the extent this rejection is directed to an alleged lack of enablement for the treatment of Huntingdon's Disease, this rejection is overcome by the accompanying Declaration of Steven A. Goldman under 37 C.F.R. § 1.132 ("Goldman Declaration").

Dr. Goldman's laboratory has found that viral overexpression of brain-derived neurotrophic factor ("BDNF") in the normal adult mammalian ventricular system induces the generation of new neurons from the progenitor cell population of the ventricular subependyma (Goldman Declaration ¶ 4). The new neurons migrate to the olfactory bulb primarily, but a large cohort invades the neostriatum as well, wherein they integrate as new neurons (Id.). These cells adopt a DARPP32/ GABAergic/calbindin^{+} phenotype, characteristic of the medium spiny neuronal

population of the caudate-putamen (Id.). Since this is the predominant neostriatal phenotype lost in Huntington's Disease, Dr. Goldman postulated that the induced generation of this cell type could slow or reverse disease progression.

Dr. Goldman and his students had this strategy for treatment of Huntington's Disease tested in a transgenic model of Huntington's Disease known as the R6/2 mouse (Goldman Declaration ¶5). This mouse has been engineered to express a 150 repeat polyglutamine expansion in the first exon of the ht gene (Mangiarini et al. Cell 87:493-506 (1996)) (Id.). The mutant mouse develops increasing spasticity beginning by 6-8 weeks of age, exhibits striatal degeneration and intranuclear inclusions, and typically dies by 12-14 weeks of age (Id.). These traits make it an attractive target for cell-based therapeutic strategies, in that its baseline deterioration is both rapid and reproducible, providing a clear time frame within which therapeutic strategies may be best evaluated (Id.).

To test the feasibility of using an adenovirus containing a BDNF coding sequence ("AdBDNF") to induce striatal neurogenesis to treat Huntington's Disease, students in Dr. Goldman's laboratory working under his direction injected AdBDNF intraventricularly into Huntington mutant R6/2 mice and into normal wild-type mice (Goldman Declaration ¶6). The results are described below (Id.).

The huntingtin mutant R6/2 mouse brain continued to harbor competent neuronal progenitor cells which can give rise to striatal neurons in response to AdBDNF infection of the ventricular zone (Goldman Declaration ¶7). Dr. Goldman's laboratory determined that >140 new medium spiny neurons/mm^3/2-3 weeks, or by extrapolation 2,400-3,640/mm^3/year, may be induced in response to AdBDNF (Id.).

The normal wild-type mouse neostriatum harbors approximately 40,000 neurons/mm^3 (Goldman Declaration ¶8). Against this baseline, huntingtin mutant mice of the same strain and genetic background lose >10% of their striatal neurons by 8 weeks of age, and >15% by 12 weeks (quantification of these figures in the 12 week transgenic mouse is ongoing; these mice typically die by 12-14 weeks) (Id.). Dr. Goldman's data suggests that with an appropriately long-lasting expression vector, a majority of the lost striatal neuronal population may be regenerated in response to BDNF, on an annualized basis (Id.). Moreover, Dr. Goldman anticipates that when used in conjunction with strategies intended to expand the underlying neural progenitor population, BDNF overexpression can induce regeneration of

medium spiny neurons in the huntingtin brain more rapidly than they are lost to the underlying disease process (Id.).

By labeling the newly generated neostriatal neurons by injection of a retrograde tracer into the globus pallidus, which is the normal target of neostriatal medium spiny neurons, it was found that >40% of the newly-generated striatal neurons extended fibers to their targets in the globus pallidus by 7 weeks (Goldman Declaration ¶9). Dr. Goldman expected even higher proportions of neostriatal neurons to extend fibers and connect to their target neurons at longer time points (Id.).

The new neurons survived after their initial generation, with no significant fall in newly generated neurons between 3 and 8 weeks after being generated (Goldman Declaration ¶10).

On the basis of these observations, Dr. Goldman believes there is a reasonable likelihood that the increment in new medium spiny cells regenerated in response to AdBDNF treatment will be sufficient to yield a deceleration of the disease course, as reflected in a diminished morbidity and/or mortality (Goldman Declaration ¶11). Proof of this contention in humans will need to await clinical trials of BDNF overexpression vectors in Huntington's Disease patients (Id.). That being said, Dr. Goldman is optimistic that this strategy will indeed prove beneficial in either slowing the disease course, or otherwise beneficially affecting the clinical status of these patients (Id.).

With regard to neurotrophic factors generally, Dr. Goldman believes that this demonstration of the inducibility of endogenous neural progenitor cells provides both a conceptual and operational basis for using neurotrophins besides BDNF, as well as gene delivery of such other neurotrophins, to stimulate endogenous progenitor cells of the adult brain, for the purpose of regenerating neural cell populations lost to disease or injury (Goldman Declaration ¶ 12). An example in support of this has recently been published by Nakatomi et al., Cell 110:429-41 (2002) which reported that FGF may be used to induce production of new hippocampal pyramidal neurons (Id.).

Finally, the present application teaches (on pages 10 - 11 and 15 – 19) how to prepare constructs with the requisite control elements for the therapeutic administration of genes encoding neurotrophic factors. The transduction and selection of viruses with these constructs for such administration are described on pages 11- 15 of the present application. The doses and modes of administration

necessary for carrying out the therapeutic administration of genes encoding neurotrophic factors in accordance with the present invention is described on pages 20 - 21. From such disclosure of the present application, one of ordinary skill in the art would be fully able to practice the present invention of treating Huntingdon's Disease. Although experimentation would be needed to optimize suitable doses and modes of administration, such additional work is conventionally carried out in developing therapeutics and would not require anything more than routine experimentation.

For all of these reasons, the rejection of claims 28-30, 33-40, and 44-47 under 35 U.S.C. § 112 (1st para.) for lack of enablement should be withdrawn.

The rejection of claims 1-9, 13-21, and 25-27 under 35 U.S.C. § 112 (1st para.) for lack of enablement is respectfully traversed in view of the above amendments.

The rejection of claim 26 under 35 U.S.C. § 112 (2nd para.) for indefiniteness is respectfully traversed in view of the above amendments.

The rejection of claims 1-5, 7, 13-17, 19, and 25 under 35 U.S.C. §102(e) as anticipated by U.S. Patent No. 6,071,889 to Weiss, et. al. is respectfully traversed.

Weiss teaches a method of inducing proliferation of a multipotent neural stem cell by administering various growth factors (e.g., brain-derived neurotrophic factor) as proteins *per se* or as nucleic acids encoding such proteins. However, Weiss fails to teach injecting a nucleic acid construct encoding a neurotrophic factor "into a subject's lateral ventricles or ventricular wall zone under conditions effective to express the neurotrophic factor and to induce neuronal production in any one or all of the caudate nucleus, the putamen, and/or the globus pallidus of the subject" (as set forth in claim 1) and injecting a nucleic acid construct encoding a neurotrophic factor "into the subject's lateral ventricles or ventricular wall zone under conditions effective to express the neurotrophic factor and to recruit neurons to any one or all of the caudate nucleus, the putamen, and/or the globus pallidus of the subject" (as set forth in claim 13). Accordingly, the rejection of claims 1-5, 7, 13-17, 19, and 25 under 35 U.S.C. §102(e) for anticipation by Weiss should be withdrawn.

The rejection of claims 1-4, 7, 13-16, 19, and 25 under 35 U.S.C. §102(a) as anticipated by Benraiss, et. al., "*In Vivo* Transduction of the Adult Rat Ventricular Zone with An Adenoviral BDNF Vector Increases Neuronal Production

and Recruitment to the Olfactory Bulb", Soc. Neurosci. 25: 413.3 (1999) ("Benraiss") is respectfully traversed.

Benraiss fails to teach injecting a nucleic acid construct encoding a neurotrophic factor "into a subject's lateral ventricles or ventricular wall zone under conditions effective to express the neurotrophic factor and to induce neuronal production in any one or all of the caudate nucleus, the putamen, and/or the globus pallidus of the subject" (as set forth in claim 1) and injecting a nucleic acid construct encoding a neurotrophic factor "into the subject's lateral ventricles or ventricular wall zone under conditions effective to express the neurotrophic factor and to recruit neurons to any one or all of the caudate nucleus, the putamen, and/or the globus pallidus of the subject" (as set forth in claim 13). Accordingly, the anticipation rejection based on Benraiss should be withdrawn.

The rejection of claims 1-4, 7, 13-16, 19, and 25 under 35 U.S.C. §103 for obviousness over Zigova, et. al., "Intraventricular Administration of BDNF Increases the Number of Newly Generated Neurons in the Adult Olfactory Bulb," Molec. & Cell. Neurosci. 11: 234-45 (1998)("Zigova") in view of Bajocchi, et. al., "Direct *In Vivo* Gene Transfer to Ependymal Cells in the Central Nervous System Using Recombinant Adenovirus Vectors," Nature Genetics 3: 229-34 (1993)("Bajocchi") and U.S. Patent No. 5,453,361 to Yancopoulos is respectfully traversed.

Zigova administers brain-derived neurotrophic factor protein to the right ventricle of adult rat brains to increase the number of newly generated neurons in the olfactory bulb. In contrast to the present invention, Zigova has nothing to do with "providing a nucleic acid construct encoding a neurotrophic factor" and fails to teach either injecting a nucleic acid construct encoding a neurotrophic factor "into a subject's lateral ventricles or ventricular wall zone under conditions effective to express the neurotrophic factor and to induce neuronal production in any one or all of the caudate nucleus, the putamen, and/or the globus pallidus of the subject" (as set forth in claim 1) or injecting a nucleic acid construct encoding a neurotrophic factor "into the subject's lateral ventricles or ventricular wall zone under conditions effective to express the neurotrophic factor and to recruit neurons to any one or all of the caudate nucleus, the putamen, and/or the globus pallidus of the subject" (as set forth in claim 13). As to independent claims 28 and 44, there is no suggestion in Zigova of "injecting the nucleic acid construct into a subject's lateral ventricles or

ventricular wall zone under conditions effective to treat a neurodegenerative condition" (as set forth in claim 28) or "introducing a neurotrophic factor into any one or all of a subject's caudate nucleus, putamen, and/or globus pallidus under conditions effect to treat a neurodegenerative condition" (as set forth in claim 44).

Bajocchi teaches the *in vivo* transfer of the ß-galactosidase encoding gene into ependymal cells in the central nervous system of a rat using a recombinant adenovirus vector. There is no suggestion in this reference that such administration of a gene would be useful in inducing neuronal production in any one or all of the caudate nucleus, the putamen, and/or the globus pallidus of the subject, recruiting neurons to any one or all of the caudate nucleus, the putamen, and/or the globus pallidus of the subject, or treating a neurodegenerative condition, as claimed.

Yancopoulos merely sets forth the nucleotide sequence for brain-derived neurotrophic factor.

It would not have been obvious to combine the teachings of Zigova and Bajocchi to administer a neurotrophic factor encoding gene to a subject. Although Zigova administers the brain-derived neurotrophic factor protein itself to a subject to increase the number of neurons generated in the subject's olfactory bulb, there is no suggestion that this result would be achieved by, instead, administering the gene encoding this factor. Bajocchi simply adminsters the gene encoding ß-galactosidase and provides no assurance that the brain-derived neurotrophic factor encoding gene could similarly be administered to achieve the effects noted in Zigova. Yancopoulos simply discloses the nucleotide sequence for brain-derived neurotrophic factor and provides no basis to conclude that the gene encoding this factor could be effectively administered to a subject to increase the number of neurons generated in the subject. Thus, there is no motivation to combine Zigova, Bajocchi, and Yancopoulos.

Even if these references were combinable, which they were not, their combination would not have taught the claimed invention. In particular, all of these references alone or in combination fail to teach injecting a nucleic acid construct encoding a neurotrophic factor "into a subject's lateral ventricles or ventricular wall zone under conditions effective to express the neurotrophic factor and to induce neuronal production in any one or all of the caudate nucleus, the putamen, and/or the globus pallidus of the subject" (as set forth in claim 1) and injecting a nucleic acid construct encoding a neurotrophic factor "into the subject's lateral ventricles or

ventricular wall zone under conditions effective to express the neurotrophic factor and to recruit neurons to any one or all of the caudate nucleus, the putamen, and/or the globus pallidus of the subject" (as set forth in claim 13).

In view of the failure of the combination of Zigova, Bajocchi, and Yancopoulos to establish even a *prima facie* case of obviousness, the obviousness rejection based on these references should be withdrawn.

The rejection of claims 1, 6, 13, and 18 under 35 U.S.C. § 103 for obviousness over Weiss in view of U.S. Patent No. 5,830,858 to Rosenthal ("Rosenthal") and Zigova.

Rosenthal is cited as teaching the use of an inducible promoter. However, it does not cure any of the above-noted deficiencies of Weiss or Zigova.

One of ordinary skill in the art would have had no motivation to combine these references. Rosenthal has nothing to do with the *in vivo* administration of a neurotrophic factor or a gene encoding it. Although Weiss induces proliferation of a multipotent neural stem cell by administering various growth factors (e.g., brain-derived neurotrophic factor) as proteins *per se* or as nucleic acids encoding such proteins and Zigova teaches administering the brain-derived neurotrophic factor protein to a subject's brain, there is no assurance that Weiss' use of nucleic acids encoding growth factors to induce proliferation of multipotent stem cells would be useful in carrying out Zigova's procedure of increasing the number of newly generated neurons in the olfactory bulb. The olfactory bulb and region of the brain where neural stems reside are distinct, and there is no basis to assume that teachings of administering an agent to one region of the brain are relevant to the administration of agents to a distinct part of the brain. Accordingly, there is no basis to combine Weiss, Rosenthal, and Zigova.

Even if these references were combinable, which they are not, their combination would fail to teach injecting a nucleic acid construct encoding a neurotrophic factor "into a subject's lateral ventricles or ventricular wall zone under conditions effective to express the neurotrophic factor and to induce neuronal production of any one or all of the caudate nucleus, the putamen, and/or the globus pallidus of the subject" (as set forth in claim 1) and injecting a nucleic acid construct encoding a neurotrophic factor "into the subject's lateral ventricles or ventricular wall zone under conditions effective to express the neurotrophic factor and to recruit neurons to any one or all of the caudate nucleus, the putamen, and/or the globus

pallidus of the subject" (as set forth in claim 13). The neostriatum and the olfactory bulb are distinct parts of the brain, and there is no reason to believe that a procedure of inducing neuron production in one of these locations will be effective in doing so in the other.

Due to the failure of the combination of Weiss, Zigova, and Rosenthal to establish even a *prima facie* case of obviousness, the obviousness rejection based on these references should be withdrawn.

In view of all the foregoing, it is submitted that this case is in condition for allowance and such allowance is earnestly solicited.

Respectfully submitted,

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